Advisory Committee for Pharmaceutical Science Meeting

November 29, 2001

Individual Bioequivalence

Introduction

Over the years, assessment of bioequivalence (BE) has generally been made based on the comparison of averages between the test and reference formulations. Since early 1990s, the concept of individual BE has been promulgated by several articles in the literature for consideration to include comparisons of both means and variances. The individual BE was proposed to ensure that an individual could be switched from the reference product to the test product with unchanged efficacy and safety. After evaluating the various methodological approaches, the US Food and Drug Administration (FDA) published a preliminary draft guidance in 1997 and a draft guidance in 1999 on the proposed criteria and statistical methodology for public comments.

Despite all the advantages of the individual BE approach, a number of comments on both draft guidances expressed concerns about the new criteria. These comments were presented and resolution to the concerns was sought at several public workshops and conferences. The issues were also discussed at the Expert Panel and Advisory Committee for Pharmaceutical Science (ACPS) meetings.

After careful consideration of all the recommendations from the ACPS and Expert Panel as well as public comments, the Agency in 2000 issued a final guidance for industry entitled *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*. In this guidance, the Agency recommends non-replicated BE study designs for most orally administered immediate-release drug products and replicated BE study designs for modified-release dosage forms. The guidance maintains the average BE criterion while allows the option for a sponsor to provide rationale *a priori* for using another criterion to declare BE, e.g., the individual BE criterion for highly variable drug products.

Discussion Topics for ACPS Meeting on November 29, 2001

Discussion Topic 1

Is it reasonable and appropriate for FDA to use average bioequivalence (ABE) for market access, unless there is a compelling reason not to, for an interim period of another year until a final decision is made to use individual bioequivalence (IBE) for market access?

Discussion Topic 2

The Advisory Committee is asked to comment on the proposal that if the FDA were to use IBE for market access (when there is a compelling reason not to use ABE) during the interim period, the following conditions would apply (below).

-- The sponsor declares IBE for data analysis *a priori* in BE study protocol
-- A heterogeneous population is enrolled in the study
-- The mean Test/Reference ratio is constrained to +/- 15%
-- There are no significant subject-by-formulation interaction, SxF (> 0.15)
-- The study includes at least 24 subjects
-- The study passes the IBE criterion

Discussion Topic 3

Are there scientific, technical or other reasons not to continue with the recommendations in the General BA/BE Guidance to a) conduct replicate design studies for modified release dosage forms and for highly variable drugs, and b) to use a heterogeneous study population (at least 40% male and female subjects, and/or young and elderly subjects)?

Discussion Topic 4

The Advisory Committee is asked to comment on plans for further research programs and projects associated with the use of ABE and IBE to allow comparison of bioavailability measures and to arrive at a final conclusion and recommendation on IBE.